REMARKS

In the Office Action dated May 12, 2008, claims 1-30 and 40-45 are pending. Claims 1-11, 22-30 and 40-45 are withdrawn from consideration. Claims 12-21 are under consideration.

The Office Action raises formality objections to the specification and to claims 14, 16, 17 and 19. Claims 16-19 are rejected under 35 U.S.C. § 112, first paragraph, for allegedly adding new matter. Claims 12-21 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 19 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite. Claims 12-14 and 16-19 and 21 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by George et al. (U.S. Patent Application No. 2004/0001853) ("George"), as evidenced by Glebe et al. (*World J Gastroenterol*, 2007, 13(1): 91-103) ("Glebe"). Claims 15 and 20 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over George.

Claim Amendments

Claims 12-14, 17-19 and 21 are currently amended. Claims 15-16 are canceled. Withdrawn claims 6-8, 10, 26-28 are also amended.

Specifically, independent claim 12, as amended, recites that the POI is located in a specified location, namely, in the pre-S domain of L, at the amino terminal side of the S domain of or the S domain absent the TM1 domain of L, or N-terminally to the L polypeptide. Support for this language is found in the specification, e.g., page 22, second and third full paragraphs. Claim 12, as amended, also specifies that the claimed fusion protein associates with the VLP comprising an avian hepadnavirus S polypeptide or a functional derivative thereof. Support for this amendment is found on page 4, third and last paragraphs of the specification.

Claim 13, as amended, defines the particle-associating portion of the L protein as one of those expressly described in the specification, e.g., the bridging paragraph on pages 20-21; and first full paragraph on page 22. Similar to claim 12, claim 13 has also been amended to specify that the claimed fusion protein associates with the VLP comprising an avian hepadnavirus S polypeptide or a functional derivative thereof.

Claim 14 depends on claim 12 or 13, and defines the particle-associating portion of the L protein as consisting of a specified portion of the L polypeptide.

Claims 6-7, 10, 17-19 and 27-28 have been amended to recite "90%" identity with specified sequences, rather than "50%". Support for this amendment is found on page 23, lines 7-8 of the specification.

Claims 46-47 are added, which depend from claim 13 and delineate certain preferred particle-associating portions of the L polypeptide. Support for these new claims is found in the specification, e.g., the bridging paragraph on pages 20-21; and first full paragraph on page 22.

No new matter is introduced by the foregoing amendments.

Formal Objections

The Examiner has objected to the disclosure because of alleged informalities. Specifically, the Examiner indicates that Figure 3 and Figure 4 lack the requisite and appropriate SEQ ID NO for the sequences depicted in the figures.

In response, Applicants have amended the specification by adding the proper sequence identifiers. The newly added sequence identifiers are disclosed in the Sequence Listing and in Table I. Accordingly, no new matter has been added.

Claim 14, 16, 17 and 19 were objected to because of the following alleged informalities:

Claim 14 does not end with a period. Claim 14 has been amended and now possesses a period at the end of the claim.

Claim 14 and 16 was allegedly improper for reciting "an amino acid sequence as set forth in" instead of "the amino acid sequence as set forth in." It is assumed that the Examiner meant claims 16-17. In response, claim 16 has been deleted for unrelated purposes, and claim 17 has been amended to recite "the amino acid sequence as set forth in."

Claim 19 was allegedly improper for reciting "a sequence of nucleotides as set forth in" instead of "the sequence of nucleotides as set forth in." Claim 19 has been amended to recite "the sequence of nucleotides as set forth in."

In light of the foregoing, the formality objections to the specification and the claims are overcome. Withdrawal of the objections is respectfully requested.

35 U.S.C. § 112, First Paragraph

Claims 16-19 are rejected under 35 U.S.C. § 112, first paragraph for allegedly reciting subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Examiner alleges that claims 16-19, which recite "at least 50% identity," are not properly described in the application as originally filed, and therefore introduce new matter.

Although Applicants respectfully disagree with the rejection, claims 16-19 have been amended to recite "at least 90% identity." Support for this amendment can be found on page 23, lines 7-8 of the specification. Accordingly, the current amendment clearly does not add new matter. It is respectfully submitted that the rejection has been overcome.

Claims 12-21 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply

with the written description requirement. The Examiner contends that the claims are broadly drawn to a genus of products including "functional derivatives" of avian large envelope polypeptides that are at least "50% identical" to SEQ ID NO:7 or 9; yet in the Examiner's opinion, the specification does not provide a sufficient description of distinguishing characteristics of the derivatives. More specifically, the Examiner alleges that the specification does not identify any particular portion of SEQ ID NO:7 or 9 that must be conserved in either a functional derivative thereof, or a polypeptide that is at least 50% identical to SEQ ID NO: 7 or 9.

Although Applicants respectfully disagree with the rejection, the claims have been amended to recite "at least 90%" sequence identity, and to delete the term "functional derivatives", in respect to the recited "particle-associating portion of a large envelope polypeptide". As such, it is respectfully submitted that the genus, as presently claimed, is adequately supported by the specification in compliance with the written description requirement. Therefore, the rejection is overcome and should be withdrawn.

35 U.S.C. § 112, Second Paragraph

Claim 19 is rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite for reciting "medium stringency." The Examiner alleges that it is unclear what is meant by "medium stringency."

Applicants respectfully disagree, as the definition of "medium stringency" provided on page 32, second paragraph of the specification, which is recognized by the Examiner, is unambiguous. It is correct that "medium stringency", as defined, is not limited to a single specific condition. The definition provided in the specification is consistent with the understanding of those skilled in the art, and is not ambiguous. In light of the specification, those skilled in the art would be able to identify and determine what conditions are encompassed by "medium

stringency", and whether a particular condition constitutes "medium stringency" as defined in the present application. Withdrawal of the rejection is therefore respectfully requested.

35 U.S.C. § 102(e)

Claims 12-14 and 16-19 and 21 are rejected under 35 U.S.C. §102(e) as allegedly anticipated by George et al. (U.S. Patent Application No. 2004/0001853) ("George"), as evidenced by Glebe et al. (*World J Gastroenterol*, 2007, 13(1): 91-103) ("Glebe").

According to the Examiner, George discloses constructs comprising DHBV PreS or PreS/S and a protein of interest, namely, the Fc portion of antibody (see Figure 16 and Example 5, 6 and 31). The Examiner alleges that the protein construct can assemble into VLPs because it contains all of the large envelope polypeptide (L), which is also known as PreS as evidenced by Glebe (see Figure 2 of Glebe). George further discloses SEQ ID NOs: 43 and 44, which allegedly comprise instant SEQ ID NOs: 6 and 8, and SEQ ID NOs: 7 and 9, respectively.

Although not in agreement with the Examiner, the claims have been amended to include features that are neither explicitly nor inherently disclosed by George. Accordingly, the amendments are believed to overcome the anticipation rejection based on George.

Specifically, independent claim 12, as amended, recites that the POI is located in a specified location, namely, in the pre-S domain of L, at the amino terminal side of the S domain of L or the S domain absent TM1, or N-terminally to the L polypeptide. In this regard, it is observed that George discloses hybrid proteins, as graphically depicted in Figure 16 and also described in Figures 17-18 and 20-21, wherein the Fc domain is placed downstream to the C-terminus of either the full length L polypeptide or the PreS domain alone of the L polypeptide of DHBV. Applicants note that the sequences of the PreS domain shown in Figures 17-18 of George correspond to sequences set out in SEQ I DNOS: 10-11 of the subject application and do not include the S

domain of L as set out in SEQ ID NOS: 8-9 of the subject application. SEQ ID NOS: 43-44 of George (also set forth in Figures 20-21 of George), provide the nucleotide and amino acid sequences of the PreS/S protein, i.e., the full-length L set out in SEQ ID NOS: 6 and 7 of the subject application. Applicants respectfully submit that George does not teach a fusion protein wherein a POI is placed at any of the locations as presently recited in claim 12. Therefore, on this basis alone, the fusion protein of claim 12 is novel over George.

Claim 14, as amended, defines that the particle-associating portion of the fusion protein "consists of" the S domain of L, or various specified derivatives of the S domain of L. As submitted above, the hybrid polypeptides of George include either the PreS domain of L or the full-length L. George does not teach or suggest anywhere the use of the S domain or derivatives of the S domain of L as the particle-associating portion of a fusion protein. As such, claim 14 and claims 17-19, all directed to fusion proteins based on employing the S domain or its derivatives as the particle-associating portion, are novel over George.

Claim 13, as amended, defines the particle-associating portion of the L protein as one of those expressly described in the specification, e.g., the bridging paragraph on pages 20-21; and first full paragraph on page 22. Both claims 12 and claim 13 are also amended to specify that the claimed fusion protein associates with the VLP comprising an avian hepadnavirus S polypeptide or a functional derivative thereof.

The Examiner alleges that George's fusion protein forms VLPs merely because it contains the entire L protein. Therefore, the Examiner's rejection based on George relies on an inherency theory. A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). It must be

further appreciated that "the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." Ex parte Levy, 17 USPQ2d 1461, 1464 (B.P.A.I. 1990) (Emphasis added). In the present case, the fusion proteins of George do not necessarily associate with a VLP comprising an S polypeptide, as recited in the present claims.

The relevant fusion proteins disclosed by George include the mouse Fc portion of immunoglobulin fused to the C-terminus of either the PreS domain of the L or the full length L protein. See DHBV-PreS-TBD shown in Fig. 17b, and DHBV PreS/S-TBD shown in Fig. 20b of George.

With respect to DHBV-PreS-TBD shown in Fig. 17b of George, this fusion protein does not contain the portions of the S domain of L found by the present invention to be required for association with VLPs. Therefore, this fusion protein lacking the entire S domain simply cannot associate with VLPs, regardless of what POI is used.

With respect to DHBV PreS/S-TBD shown in Fig. 20b of of George, as discussed below, it is highly unlikely that such fusion protein forms VLPs. Figs. 1 to 3a in George provide a schematic illustration of George's conceived fusion polypeptides containing antigenic sequences. A critical aspect of George's conception is the retention of disulfide bonding between the Fc portions of the monomeric polypeptides. The hinge region of the Fc domain contains two disulfide linkages that covalently link the two fusion polypeptides into a dimer (see George, paragraph [0115]). Additional disulfide linkages in C_H2 and C_H3 serve to attain and retain the proper folded conformation of each Fc domain. It is noted that although the S domain is present in this fusion of George, the particle associating properties of the S domain would most likely be negated by the constraints of the Fc domain's four disulfide bonds. It is further noted that during VLP formation,

the L and S proteins do not form homodimers. Further, George's proposed chimeric polypeptide adds 285 amino acids (the entire Fc) to the carboxy-terminus of the 328 amino acids of DHBV PreS/S. Thus, the mass of DHBV PreS/S comprises approximately 47.2% by weight (not including linker and the hexaHis tag) of a polypeptide having nothing to do with VLP formation. Thus, even independent of consideration of constraints imposed by the Fc domain's four disulfide bonds, those skilled in the art would consider it highly unlikely that the fusion protein of George associates with VLPs.

In sum, the Examiner has not established that attaching an entire Fc domain to the C-terminus of the L or S protein, as disclosed by George, necessarily results in a hybrid polypeptide that associates with VLPs. Accordingly, George does not explicitly or inherently anticipated currently amended claims 12-13.

In view of the foregoing, it is respectfully submitted that the rejection under 35 U.S.C. §102(e) based on George, as evidenced by Glebe, be withdrawn.

35 U.S.C. § 103(a)

Claims 15 and 20 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over George. The Examiner alleges that although George does not teach that the protein of interest is at the locations recited in claim 15 or that the L polypeptide comprises a signal sequence, it is well within the purview of one of ordinary skill in the art to create chimeric proteins using linkers to link the two proteins, directly fusing the two proteins (without linkers), insert one protein in a non-essential region of the second protein. Further, because many proteins, including chimeric proteins, are expressed in eukaryotic cells, it is also well within the purview of one of ordinary skill in the art to add the appropriate signal sequence to direct the protein through a specific pathway, e.g., the secretory pathway. Therefore, the Examiner concludes that it would have been obvious to

one of ordinary skill in the art to modify the construct taught by George to produce a construct where the protein of interest is located in the L polypeptide and/or the L polypeptide further comprises a signal sequence.

In response, it is respectfully noted that claim 15 has been canceled, thereby rendering the rejection under 35 U.S.C. § 103(a) relevant only to claim 20.

In the first instance, Applicants reassert that George fails to teach the fusion protein as presently recited in claims 12-14 and 17-19, as discussed above. There is no remote suggestion in George to arrive at the presently claimed fusion proteins, especially the fusion proteins as presently characterized as a protein that "associates with" VLPs. Therefore, the premise for the Examiner's obviousness rejection based on George no longer exists.

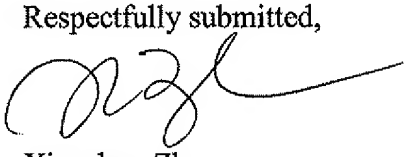
Further, George does not provide any teaching or suggestion of using a signal sequence. Further, George does not examine secretion of any fusion polypeptides because the polypeptides are purified after lysing insect cells under denaturing conditions. See e.g., George, Example 12. Under the conditions taught by George, there is no secretion and no need of a signal sequence.

Accordingly, persons of ordinary skill in the art would not consider it to be obvious, in fact, would not have any reason or motivation, to add a signal sequence to the polypeptides as presently claimed. It is respectfully submitted that the rejection under 35 U.S.C. §103(a) should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is firmly believed that the subject application is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,



Xiaochun Zhu
Registration No. 56,311

SCULLY, SCOTT, MURPHY & PRESSER, P.C.
400 Garden City Plaza-Suite 300
Garden City, New York 11530
(516) 742-4343
XZ/TG:ab